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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,419	07/09/2001	Calvin C. Hale	UMO 1531.1	7363

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,419	HALE ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004 and 18 April 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7 and 9-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6, 7 and 9-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's amendment received on 4/18/04 has been entered. Claims 1, 9, 10, 13, 15, 17, 18, 21 and 24 have been amended. Claims 2, 5, and 8 have been cancelled. Claims 1, 3-4, 6-7 and 9-24 are pending and are under current consideration.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 6-7, and 9-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 21 (and the claims depending therefrom) embrace insect larva infected with a baculovirus comprising a heterologous nucleic acid sequence encoding a recombinant membrane fusion protein, wherein the infected larvae are allowed to **develop for about 1 to 4 days** post infection.

The specification provides no implicit or explicit support for the context of allowing the infected larvae to develop for about 1 to 4 days post infection encompassed by the bolded clauses. The specification has only provided support for allowing the larvae to develop for 3-31/2 days, 1-2 days or for no more than 4 days post

infection. This implies that larvae may be allowed to develop for 1 to 4 days post-infection. However, the term "about 1 to 4 days" recited in the claims could be interpreted to mean that larvae may be allowed to develop for more than 4 days; 4 ½ days can be reasonably interpreted to mean about 4 days. The specification has not provided support for allowing larvae to develop for more than 4 days. Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*

[or point to case law supporting incorporation of such a limitation as in the instant case]".

The previous written description and enablement rejections have been withdrawn in light of the amendments to the claims; the claims now recite baculovirus vector as the means for infecting insect larvae.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The previous rejections of claims 19-20 are maintained for the reasons of record advanced on pages 9-10 of the Office action mailed on 10/18/02.

Applicant's arguments filed 4/18/04 have been fully considered but they are not persuasive. With respect to claim 19, Applicants argue the specification defines "biological activity substantially the same as the native form of the protein" as meaning that "the recombinant fusion protein produced by the method of the current invention is capable of performing substantially the same function as the native form of the protein". See page 8 of the amendment.

In response, the Examiner maintains that "substantially the same" is a relative term that renders the claim indefinite because it is not understood if the recombinant protein has the same biological activity as the native form of the protein. The term substantially does not confer a meaning of identical. The degree of similarity between the biological activities of the recombinant and native proteins is not understood given the definition provided by the specification. Does the recombinant protein possess the same biological activity as the native protein?

Accordingly, the rejection is maintained for the reasons of record.

Applicant's arguments filed 4/18/04 have been fully considered but they are not persuasive. With respect to claim 20, Applicants argue the specification defines "structurally substantially the same as the native form of the protein" as meaning that "the recombinant fusion protein produced by the method of the current invention exhibits substantially the same tertiary and quaternary structure as the native form of the protein". See page 9 of the amendment.

In response, the Examiner maintains that "substantially the same" is a relative term that renders the claim indefinite because it is not understood if the recombinant protein has the same structure as the native form of the protein. The term substantially does not confer a meaning of identical. The degree of similarity between the structures of the recombinant and native proteins is not understood given the definition provided by the specification. Does the recombinant protein possess the same structure as the native protein?

The following new grounds of rejection under 35 U.S.C. 112, 2nd paragraph have been necessitated by the claim amendments:

Claim 7 is indefinite as written. The claim embraces the insect larvae of claim 1, wherein the larvae are in the early fourth instar stage of development. However, claim 1 recites two different insect larvae: infected and uninfected. Accordingly, claim 7 is indefinite because is not clear which larvae (infected or uninfected) are in the early fourth instar stage of development. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claims 21-23 under 35 U.S.C. 102(b) as being anticipated by Pandit et al is withdrawn in light of the amendments to the claims, particularly with respect to newly added steps (d) and (e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4, 6-7, 9-12, 19-21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onda et al (US 5,858,787) taken with Cha et al (A, Biotechnol. Prog.) and Cha et al (B, Biotechnol. Bioeng).

The claims are directed to methods for producing a recombinant membrane protein in an insect larvae expression system, comprising infecting larvae with a baculovirus vector comprising a nucleic acid sequence encoding a recombinant membrane fusion protein with an affinity tag, wherein the protein is expressed in larvae and purified by affinity chromatography, and wherein the affinity tag is poly (His), and wherein the larvae are allowed to develop for 1 to 4 days post-infection and homogenate of larvae is separated into a membrane-containing portion, which contains the recombinant membrane fusion protein, and soluble portion, and wherein the membrane-containing is solubilized prior to purification by affinity chromatography. The claims are further directed to infecting the larvae at the fourth instar stage of development, centrifuging an extract from larvae to isolate a fraction comprising the recombinant membrane fusion protein and infecting the insect larvae by injecting the vector.

Onda et al teach production of a pituitary adenylate cyclase activating polypeptide receptor (PACAPr). Onda et al isolation of a nucleic acid sequence encoding a PACAPr (see columns 3-4) and contemplate the PACAPr could be produced in insect larvae (line 19), recombinant bacteria, yeast, or animal cells (see column 26). In column 32, beginning in line 2, Onda et al teach that a baculovirus vector may be used to introduce PACAPr encoding DNA into host cells [insect cells].

Onda et al teach that recombinant PACAPr is purified as follows: a cellular homogenate is prepared and centrifuged to produce a membrane-containing portion and a soluble portion; the membrane-containing portion is solubilized; and the solubilized membrane-containing portion is run through an affinity chromatography column to produce purified PACAPr. See columns 32-33 and 38. Onda et al teach that the sequence of recombinant PACAPr can be modified by introduction of a cysteine tag, which is biotinylated to facilitate purification by affinity chromatography. See columns 22-23. In addition, Onda et al teach various assays for identifying physical characteristics of recombinant PACAPr. The antagonist screening method discussed in columns 53-58 can be broadly interpreted to read on identifying a physical characteristic of a recombinant membrane protein. A physical characteristic of recombinant membrane protein can be its ability to bind an antagonist. Such an interpretation is correct given the claim is not limited to identification of any particular physical characteristic. Given the results of the antibody binding assays in columns 57-58, it appears that recombinant PACAPr has substantially the same structure and biological activity as native PACAPr.

Onda et al do not teach use of a histidine tag for affinity purification or development of insect larvae 1 to 4 days post-infection.

However at the time the claimed invention was made, methods of using insect larvae to produce recombinant fusion proteins were within the routine skill level of the ordinary artisan. In particular, use of tags, such as a histidine tag, for facilitation of affinity purification and development of insect larvae 1 to 4 days post-infection with respect to production of recombinant fusion proteins in insect larvae were within the

purview of one of ordinary skill in the art as evidenced by Cha et al (A, Biotechnol. Prog.) and Cha et al (B, Biotechnol. Bioeng). It is noted that although Cha (A) and Cha (B) do not teach production of recombinant membrane fusion proteins in insect larvae, absent evidence to the contrary, one of ordinary skill in the art would have a reasonable expectation that the methodology of Cha (A) and Cha (B), particularly use of histidine tags or development of insect larvae 1 to 4 days post-infection could be extrapolated to encompass production of recombinant membrane fusion proteins.

Cha et al (A) teach a production of fusion proteins comprising a histidine affinity ligand [for simplified purification using affinity chromatography], gfp, and enterokinase cleavage site [for recovery of the product from the fusion], and the product [protein of interest, demonstrating by way of example Cha et al taught purification of human interleukin-2 (hIL-2)]. See Figure 1 on page 283. Cha et al teach that a nucleotide sequence encoding such a fusion protein is inserted into a baculovirus vector, which was then used to infect insect larvae at the fourth instar stage of development. See the Materials and Methods section: Strains and Recombinant Baculoviruses beginning on page 283 and bridging to page 284. Cha et al go on to report that the larvae are homogenized in a buffer to produce a homogenate containing the fusion protein. The homogenate is then centrifuged to remove debris and the supernatant comprising the fusion protein is used for purification. See the Materials and Methods section: Sample Preparation and Storage on page 284. The fusion protein was then affinity purified on an affinity column by immobilized metal affinity chromatography (IMAC). See page 284 column 2. Purified fusion protein is then eluted from the IMAC column. The fractions

containing the fusion protein can be visualized by examining the fluorescence of the GFP under UV light. See figure 3 on page 285. The eluted purified samples were then assayed by SDS-PAGE and Western blot. The purified fusion protein was then cleaved by an enterokinase to separate hIL-2 from the GFP/His. See Figure 5 on page 285 as well as column 2 on page 285. Cha et al discuss that the hIL-2 was cloned in frame (see page 285, the first line of the Conclusion section), which can be interpreted to mean that recombinantly produced hIL-2 would have substantially the same structure and activity as the native form of hIL-2. In addition, Cha et al (B) reports that expression profile of recombinant GFP was examined at 60, 74 and 84 hours post infection; expression of GFP was detected at 74 and 84 hours. See page 319, in the paragraph bridging columns 1-2. Cha et al (B) also reports that infection of the insect larvae may be accomplished by injecting a recombinant virus into the cuticle of insect larvae. See page 317, column 1 at the beginning of the first full paragraph.

Accordingly, in view of the routine state of the art of recombinant protein production in insect larvae as presented by Cha (A) and Cha (B), it would have been obvious to produce a recombinant PACAPr fusion protein in insect larvae, particularly a fusion protein comprising a histidine tag, wherein the insect larvae are allowed to develop 1 to 4 days post-infection. One of ordinary skill in the art would have been sufficiently motivated to produce such a PACAPr fusion protein because it was an art-recognized goal to produce recombinant PACAPr as taught by Onda, and in particular to use insect larvae as discussed by Onda (see column 26), and more particularly because the methods of protein production in insect larvae as exemplified by Cha (A)

and Cha (B) have a general utility for rapid and identification and purification of recombinant proteins expressed by baculovirus (see Cha (A) on page 286) and because affinity tags, such as histidine, are not unobvious as they are routinely used in protein purification. One of ordinary skill in the art would have been sufficiently motivated to allow insect larvae to develop 1 to 4 days post-infection because Cha (B) discuss that expression of recombinant GFP is detected in insect larvae at 74 and 84 hours post-infection.

Thus, the claimed invention, as a whole, was clearly prima facie obvious in the absence of evidence to the contrary.

With respect to Cha (A) and Cha (B), Applicants arguments received on 4/18/04 have been fully considered but they are not persuasive. Applicants have argued Cha (A) and Cha (B) fail to disclose production of recombinant membrane proteins. In particular Applicants argue neither Cha (A) nor Cha (B) disclose separation of an insect larvae homogenate into a membrane-containing portion, which comprises the recombinant membrane protein of interest, and a soluble portion or solubilization of the membrane-containing portion prior to affinity purification. Applicants assert that neither Cha (A) nor Cha (B) suggest that their methodology could be applied to recombinant membrane proteins. See pages 14-15 of the amendment.

In response, the Examiner maintains the collective teachings of Cha (A) and Cha (B) are relevant. For example, for the purpose of the instant rejection, the teachings of Cha (A) and Cha (B) are relied upon for the following reasons: 1) use of a histidine tag;

2) development of insect larvae for 1 to 4 days post-infection; 3) use of fourth instar insect larvae for infection; and 4) removal of the histidine tag. It is correct that Cha (A) and Cha (B) do not teach production of recombinant membrane proteins. However, use of histidine tags for affinity purification (as well as their subsequent removal) or development of insect larvae for 1 to 4 days post-infection or use of fourth instar insect larvae for infection are not patentable limitations. Such limitations are routine and obvious. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Claims 1, 12, 13 and 15 rejected under 35 U.S.C. 103(a) as being unpatentable over Onda taken with Cha (A) and Cha (B) as applied to claims 1, 3-4, 6-7, 9-12, 19-21 and 24 above, and further in view of Au-Young and Goli.

The claims are directed to methods of producing transport and channel-forming proteins in insect larvae.

Onda et al teach production of a pituitary adenylate cyclase activating polypeptide receptor (PACAPr). Onda et al isolation of a nucleic acid sequence encoding a PACAPr (see columns 3-4) and contemplate the PACAPr could be produced in insect larvae (line 19), recombinant bacteria, yeast, or animal cells (see

column 26). In column 32, beginning in line 2, Onda et al teach that a baculovirus vector may be used to introduce PACAPr encoding DNA into host cells [insect cells]. Onda et al teach that recombinant PACAPr is purified as follows: a cellular homogenate is prepared and centrifuged to produce a membrane-containing portion and a soluble portion; the membrane-containing portion is solubilized; and the solubilized membrane-containing portion is run through an affinity chromatography column to produce purified PACAPr. See columns 32-33 and 38. Onda et al teach that the sequence of recombinant PACAPr can be modified by introduction of a cysteine tag, which is biotinylated to facilitate purification by affinity chromatography. See columns 22-23. In addition, Onda et al teach various assays for identifying physical characteristics of recombinant PACAPr. The antagonist screening method discussed in columns 53-58 can be broadly interpreted to read on identifying a physical characteristic of a recombinant membrane protein. A physical characteristic of recombinant membrane protein can be its ability to bind an antagonist. Such an interpretation is correct given the claim is not limited to identification of any particular physical characteristic. Given the results of the antibody binding assays in columns 57-58, it appears that recombinant PACAPr has substantially the same structure and biological activity as native PACAPr.

However at the time the claimed invention was made, methods of using insect larvae to produce recombinant fusion proteins were within the routine skill level of the ordinary artisan. In particular, use of tags, such as a histidine tag, for facilitation of affinity purification and development of insect larvae 1 to 4 days post-infection with respect to production of recombinant fusion proteins in insect larvae were within the

purview of one of ordinary skill in the art as evidenced by Cha et al (A, Biotechnol. Prog.) and Cha et al (B, Biotechnol. Bioeng). It is noted that although Cha (A) and Cha (B) do not teach production of recombinant membrane fusion proteins in insect larvae, absent evidence to the contrary, one of ordinary skill in the art would have a reasonable expectation that the methodology of Cha (A) and Cha (B), particularly use of histidine tags or development of insect larvae 1 to 4 days post-infection could be extrapolated to encompass production of recombinant membrane fusion proteins.

Cha et al (A) teach a production of fusion proteins comprising a histidine affinity ligand [for simplified purification using affinity chromatography], gfp, and enterokinase cleavage site [for recovery of the product from the fusion], and the product [protein of interest, demonstrating by way of example Cha et al taught purification of human interleukin-2 (hIL-2)]. See Figure 1 on page 283. Cha et al teach that a nucleotide sequence encoding such a fusion protein is inserted into a baculovirus vector, which was then used to infect insect larvae at the fourth instar stage of development. See the Materials and Methods section: Strains and Recombinant Baculoviruses beginning on page 283 and bridging to page 284. Cha et al go on to report that the larvae are homogenized in a buffer to produce a homogenate containing the fusion protein. The homogenate is then centrifuged to remove debris and the supernatant comprising the fusion protein is used for purification. See the Materials and Methods section: Sample Preparation and Storage on page 284. The fusion protein was then affinity purified on an affinity column by immobilized metal affinity chromatography (IMAC). See page 284 column 2. Purified fusion protein is then eluted from the IMAC column. The fractions

containing the fusion protein can be visualized by examining the fluorescence of the GFP under UV light. See figure 3 on page 285. The eluted purified samples were then assayed by SDS-PAGE and Western blot. The purified fusion protein was then cleaved by an enterokinase to separate hIL-2 from the GFP/His. See Figure 5 on page 285 as well as column 2 on page 285. Cha et al discuss that the hIL-2 was cloned in frame (see page 285, the first line of the Conclusion section), which can be interpreted to mean that recombinantly produced hIL-2 would have substantially the same structure and activity as the native form of hIL-2. In addition, Cha et al (B) reports that expression profile of recombinant GFP was examined at 60, 74 and 84 hours post infection; expression of GFP was detected at 74 and 84 hours. See page 319, in the paragraph bridging columns 1-2. Cha et al (B) also reports that infection of the insect larvae may be accomplished by injecting a recombinant virus into the cuticle of insect larvae. See page 317, column 1 at the beginning of the first full paragraph.

The collective teachings of Onda et al, Cha (A) and Cha (B) do not discuss production of transport or channel-forming membrane fusion proteins.

However, at the time the claimed invention was made it was routine in the art to produce transport and channel-forming membrane fusion proteins in insect larvae. Au-Young teach that PLHu is a membrane protein that is a member of the class of small hydrophobic transport-related proteolipids containing four alpha-helical transmembrane domains. See column 4, lines 43-45. Au-Young teach that biologically active PLHu can be produced by inserting the nucleotide sequence encoding PLHu into an expression vector of choice for use in an appropriate host system. See column 8, lines 28-54. Au-

Young contemplate that a method of producing human proteolipid (PLHu) would comprise an insect larvae expression system, comprising infecting Trichoplusia larvae with an Autographa californica nuclear polyhedrosis virus (AcNPV, which is a baculovirus) vector comprising the coding sequence of PLHu (see column 9, beginning in line 56 and bridging to column 10 through line 2). Goli et al teach that HCCP is a human chloride channel. See column 7 lines 47-51. Goli et al teach that biologically active HCCP can be produced by inserting the nucleotide sequence encoding HCCP into an expression vector of choice for use in an appropriate host system. See column 11, beginning on line 55 and bridging to column 12, through line 15. Goli et al contemplate that a method of producing HCCP would comprise an insect larvae expression system, comprising infecting Trichoplusia larvae with an Autographa californica nuclear polyhedrosis virus (AcNPV, which is a baculovirus) vector comprising the coding sequence of HCCP (see column 13, lines 16-28).

Accordingly, in view of the routine state of the art of protein production in insect larvae as presented by Onda, Cha (A) and Cha (B), it would have been obvious to produce a recombinant transport or channel-forming membrane fusion protein in an insect larvae system. One of ordinary skill in the art would have been sufficiently motivated to produce a transport or channel-forming membrane fusion protein in an insect larvae system because it was an art-recognized goal to produce channel-forming membrane proteins in insect larvae, such as recombinant HCCP as taught by Goli et al (see column 11, beginning on line 55 and bridging to column 12, through line 15, and

column 13) or transport membrane proteins in insect larvae, such as recombinant PLHu as taught by Au-Young (see column 8, lines 28-54 and column 9).

Thus, the claimed invention, as a whole, was clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments filed 4/18/03 have been fully considered but they are not persuasive. With respect to Au-Young and Goli, Applicants have argued that neither teaches production of recombinant proteins in the context of an insect system but rather both provide examples of protein production in other systems.

In response, the Examiner asserts that both Au-Young and Goli contemplated production of their respective proteins in insect larvae. Therefore, it would have been obvious to produce the proteins of Au-Young and Goli in insect larvae given the collective teachings of Onda, Cha (A) and Cha (B). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, general knowledge for production of recombinant membrane fusion proteins was available to one of ordinary skill in the art as evidenced by Onda,

Cha (A) and Cha (B). Motivation for producing transport or channel-forming membrane proteins in insect larvae was provided by both Au-Young and Goli as discussed above.

Applicant's arguments with respect to Cha (A) and Cha (B) were previously discussed. Please see above.

Sequence Compliance

The instant application is now in compliance with the sequence rules.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER